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Metabolism in the Tumor Microenvironment

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Abstract

Experiments in culture systems where one cell type is provided with abundant nutrients and oxygen have been used to inform much of our understanding of cancer metabolism. However, many differences have been observed between the metabolism of tumors and the metabolism of cancer cells grown in monoculture. These differences reflect, at least in part, the presence of nonmalignant cells in the tumor microenvironment and the interactions between those cells and cancer cells. However, less is known about how the metabolism of various tumor stromal cell types differs from that of cancer cells, and how this difference might inform therapeutic targeting of metabolic pathways. Emerging data have identified both cooperative and competitive relationships between different cell types in a tumor, and this review examines how four abundant stromal cell types in the tumor microenvironment, fibroblasts, T cells, macrophages, and endothelial cells, contribute to the metabolism of tumors.

INTRODUCTION

The word "stroma" comes from the Greek word for layer or covering, speaking to the role of stroma in defining the structure of tissues. In cancer biology, "stroma" refers to the nonmalignant cells present in the tumor microenvironment. Although there is a wide range of stromal cell types, here we discuss the metabolism of four abundant types of stromal cells in tumors: fibroblasts, T cells, macrophages, and endothelial cells (**Figure 1**).

Most insights into tumor metabolism come from studies of bulk tumors and therefore represent an average of the metabolism of all cells present in the tumor. Metabolic gene expression measured by RNA sequencing (RNA-seq) in bulk tumors is different from expression measured by single-cell RNA-seq, suggesting that conclusions based on bulk tumor metabolism may not capture all aspects of cancer metabolism and may ultimately oversimplify the complex, heterogeneous composition of tumors (Xiao et al. 2019). In some tumors, such as those found in pancreatic cancer, a minority of the tumor is composed of cancer cells; as much as 90% of the tumor is composed of stroma (Feig et al. 2012).

Increased consumption of glucose and production of lactate in the presence of oxygen, known as aerobic glycolysis or the Warburg effect, has long been appreciated as a prominent metabolic phenotype of cancer (Cori & Cori 1925, Warburg 1925). Glutamine consumption and metabolism can also be an important characteristic of cancer cells (Coles & Johnstone 1962, Deberardinis et al. 2007, Rabinovitz et al. 1956, Reitzer et al. 1979); accordingly, glucose and glutamine are the two most consumed nutrients by many cancer cells in culture (Hosios et al. 2016). These metabolic characteristics have long been attributed to the cancer cells within the tumor; however, recent studies have suggested that some aspects of tumor metabolism can be quite different from the metabolism of cancer cells in culture. For example, glutamine is an important nutrient

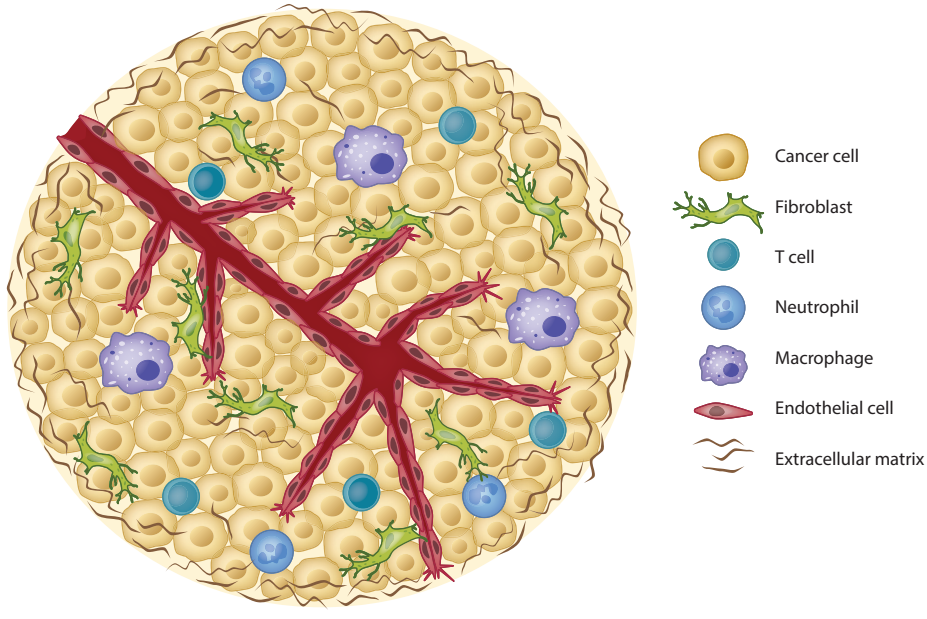

Figure 1

The tumor microenvironment consists of cancer cells as well as many different types of stromal cells, including fibroblasts, T cells, neutrophils, macrophages, and endothelial cells. Many tumors also are made up of a dense extracellular matrix, which can act as a barrier to drug delivery or as a nutrient source for tumors.

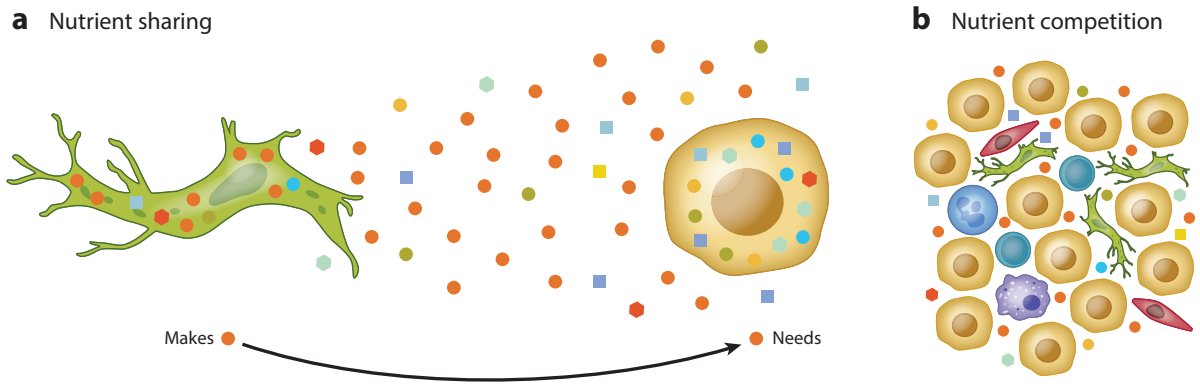

Figure 2

Metabolic interactions in the tumor microenvironment. In a nutrient sharing model (*a*), one cell type, such as a stromal fibroblast, secretes a metabolite that is needed by a second cell type, such as a cancer cell or other stromal cell type. In a nutrient competition model (*b*), cancer and stromal cells are competing for a limited amount of a metabolite available in the surrounding environment.

for most cancer cells in culture, but it is used less by some tumors in vivo (Biancur et al. 2017, Davidson et al. 2016, Muir et al. 2017, Sellers et al. 2015), and nutrients such as alanine, lactate, or ammonia have been reported to be important contributors to tumor metabolism in some contexts (Faubert et al. 2017, Hensley et al. 2016, Hui et al. 2017, Sousa et al. 2016, Spinelli et al. 2017).

CHALLENGES TO STUDYING METABOLIC INTERACTIONS IN THE TUMOR MICROENVIRONMENT

Environmental context, differences in nutrient use among cell populations, and metabolic cooperation or competition between cell types can all influence tumor phenotypes (**Figure 2**). Symbiotic (Linares et al. 2017, Sousa et al. 2016, Valencia et al. 2014) and competitive (Chang et al. 2015, Ho et al. 2015, Zecchin et al. 2017) metabolic interactions between cell types have been reported in various cancers. Although cancer cells and stromal cells can experience the same local environment with respect to extracellular nutrients, these cells may have different metabolic demands. For cancer cells to metastasize to a new distant site, an ability to adapt to a new microenvironment is needed, including both symbiotic and competitive interactions with cell types within that tissue. Some data support that stromal cells may facilitate this process (Whatcott et al. 2015), although the exact role of stroma in metastasis development is an ongoing area of study (Aiello et al. 2016, Hessmann et al. 2018).

Studies of metabolism in cultured cells are limited in that they do not model the contribution of tissue context, including the presence of multiple cell types within a tumor, the heterogeneity of both malignant and nonmalignant cells, and nutrient delivery in different regions of the tumor in vivo. The establishment of cell lines selects for fast-growing cancer cell clones that proliferate in supraphysiological nutrient and oxygen levels, abolishing population and nutrient heterogeneity known to exist in tumors (Hynds et al. 2018, Mayers & Vander Heiden 2015, Wilding & Bodmer 2014). When grown outside of their physiological context, crucial parameters such as metabolic interactions between cell types are also lost. Furthermore, it is thought that cell sorting can drastically alter the metabolism of cells from their unperturbed state (Llufrio et al. 2018), which adds another layer of difficulty in separating the metabolisms of different cell populations in tumors or

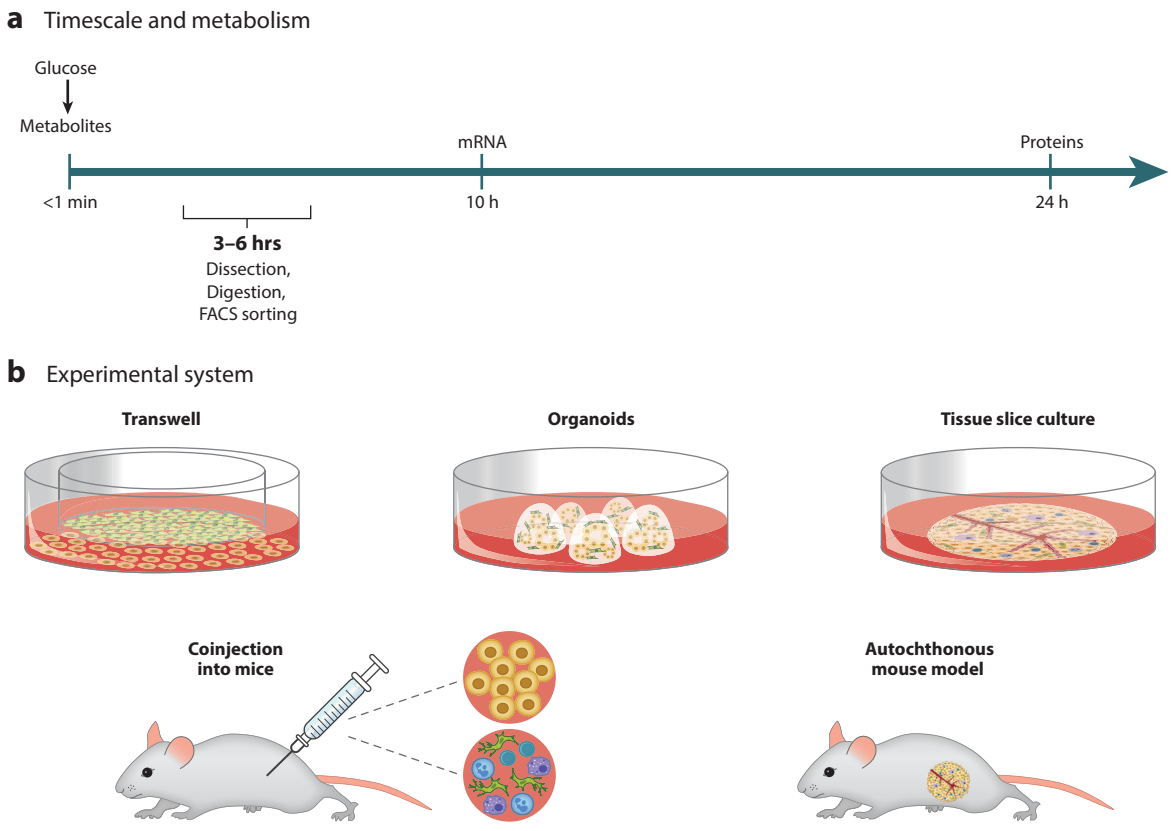

Figure 3

Challenges to studying metabolic heterogeneity. (*a*) Metabolites turn over on timescales that are faster than the time necessary to digest a tumor or coculture and perform cell sorting, presenting a challenge to studying metabolic heterogeneity in tumors. (*b*) Various experimental systems are used to study tumor heterogeneity in vitro such as transwell cultures, organoid cultures, and tissue slice cultures. In vivo, coinjection of cancer cells and stromal cells is often used to assess stromal cell function, as are autochthonous mouse models of cancer. Abbreviations: FACS, fluorescence-activated cell sorting; mRNA, messenger RNA.

in cocultures of cancer cells and stroma. Of note, most metabolic reactions occur on timescales that are much faster than the time needed to separate and analyze cells (Shamir et al. 2016), complicating the use of existing tools to assess metabolism (**Figure 3*a***).

Alternative in vitro culture systems are being developed to circumvent some limitations of two-dimensional (2D) monolayer cultures and better model the differences in metabolism observed in tumors (Muir et al. 2018) (**Figure 3*b***). For example, use of 3D organoid systems can mimic aspects of tumor biology present in human and mouse tissue, and stromal cells can be added to these organoid cultures to model some aspects of tumor heterogeneity (Boj et al. 2015, Huang et al. 2015, Li et al. 2014, Öhlund et al. 2017, Walsh et al. 2016). Tissue slice cultures, a technique previously used by Warburg in early studies of tumor metabolism (Warburg et al. 1927), can also recapitulate some of the metabolic features and cellular diversity of tumors (Fan et al. 2016, Sellers et al. 2015). Finally, efforts to more effectively study the metabolism of different cell populations in vivo and the development of media with physiological levels of nutrients can lend insights into the interactions between cells in tumors that are not possible using standard cell culture approaches (Cantor et al. 2017, Muir et al. 2017, Sullivan et al. 2019, Vande Voorde et al. 2019). Advances in

in vitro systems aimed at better mimicking tumor heterogeneity and nutrient availability will help us further understand the metabolism of tumor stromal cell types.

FIBROBLAST METABOLISM

Fibroblasts are a type of mesenchymal cell found in most tissues of the body that have a role in synthesizing extracellular matrix (ECM) proteins (**Figure 1**). ECM forms the structure of connective tissue, and production of ECM plays a key role in wound healing. These normal tissue fibroblasts can become activated during tumorigenesis, and it has been argued that they promote tumor growth and progression both by acting as a barrier to immune surveillance and drug delivery and by secreting prosurvival factors (Jacobetz et al. 2013, Neesse et al. 2013, Olive et al. 2009, Provenzano et al. 2012). Fibroblasts within tumors, commonly termed tumor- or cancer-associated fibroblasts (CAFs), are a common tumor stromal cell type that have been widely investigated to understand their effects on tumor growth.

Of note, fibroblasts can exhibit phenotype heterogeneity based on tissue location and other factors. A common fibroblast used to study interactions of cancer cells and fibroblasts is the pancreatic stellate cell (PSC), a type of pancreatic resident fibroblast that becomes activated during cancer progression and is thought to further support the tumor's growth and progression. Quiescent PSCs are characterized by the presence of lipid droplets containing vitamin A (Watari et al. 1982). Once activated, PSCs express the activation marker alpha smooth muscle actin (αSMA) and the lipid droplets disappear. These activated PSCs can secrete lipids, such as lysophosphatidylcholines, which can support tumor growth (Auciello et al. 2019). Once activated by cancer cells, these PSCs can differentiate into CAFs in the tumor microenvironment and contribute to the ECM that is found in pancreatic cancers (Bynigeri et al. 2017).

Coinjection of cancer cells with either proliferating or irradiated fibroblasts in mice has been shown to enhance tumor growth, including in contexts where cancer cells will not form tumors when transplanted alone (Camps et al. 1990, Gleave et al. 1991, Olumi et al. 1999, Picard et al. 1986, Pritchett et al. 1989). Culturing cancer cells with fibroblast-conditioned media enhances their growth (Pritchett et al. 1989), and injecting mice with fibroblast-conditioned media is sufficient to enhance tumor growth, suggesting a role for secreted factors in mediating this effect (Picard et al. 1986, Pritchett et al. 1989). Recently, fibroblasts have been shown to enhance pancreatic cancer organoid growth (Öhlund et al. 2017). However, mouse studies where fibroblasts have been genetically ablated in pancreatic tumors (Özdemir et al. 2014) or where sonic hedgehog, a ligand that stimulates fibroblasts, is deleted (Lee et al. 2014, Rhim et al. 2014) have resulted in worse tumor progression and growth, suggesting that stromal cells can also restrain progression of pancreatic cancer in certain cases. A clinical trial of a hedgehog pathway inhibitor in pancreatic cancer failed to show any benefit (Kim et al. 2014), and a recent trial showed that the addition of hyaluronidase, which degrades hyaluronic acid in the ECM, to standard chemotherapy in pancreatic cancer resulted in worse overall survival (Ramanathan et al. 2019). These studies highlight the complexity of interactions between cancer cells, the ECM present within tumors, and different stromal cell populations in tumor growth and progression.

Several possibilities for how to reconcile the pro- and anticancer properties of fibroblasts have emerged over the past few years. First, the use of autochthonous mouse models and methods where fibroblasts and cancer cells are mixed in cocultures or in vivo may yield different results (**Figure 3*b***). Furthermore, the effect of depleting fibroblasts from the tumor microenvironment is likely different from the effects of stromal reprogramming, whereby stromal cells are intact but adopt a metabolically or transcriptionally altered phenotype (Hessmann et al. 2018, Sherman et al. 2014). Additionally, multiple studies have found that there are different fibroblast subsets in the

tumor microenvironment with differential abilities to affect cancer cell proliferation in different cancers (Costa et al. 2018, Costea et al. 2013, Franco-Barraza et al. 2017, Öhlund et al. 2017, Su et al. 2018). Each of these studies highlights the importance of delineating fibroblast subpopulations in analysis of cancer cell–fibroblast interaction, and more work is needed to understand the different fibroblasts associated with each cancer type. Better functional assays are also needed to test the effect of different populations of fibroblasts on tumor growth in vivo, as fibroblasts do not persist in transplanted tumors after cotransplantation with cancer cells, suggesting an effect on tumor initiation or engraftment rather than on later stages of tumor progression (Sousa et al. 2016). Studying the facilitative role of fibroblasts in intact tumors is challenging, and understanding the contribution of different fibroblast subtypes to tumor metabolism may require better tools such as lineage tracing techniques to differentiate between different fibroblast populations in vivo.

One of the primary functions of fibroblasts is to produce and secrete ECM. Collagen, a protein rich in glycine and proline, is one of the primary proteins comprising the ECM (Kalluri 2016). It is estimated that up to 5–10% of all protein synthesis in fibroblasts is dedicated to the production of collagen (Green & Goldberg 1965, Kamine & Rubin 1977, Priest & Davies 1969). To meet the demand for production of ECM proteins, both quiescent and proliferating fibroblasts have high flux through glycolysis (Lemons et al. 2010, Nigdelioglu et al. 2016, Vincent et al. 2008, Zhao et al. 2019), although this finding has been challenged in some systems (Sousa et al. 2016, Yang et al. 2016). Fibroblasts also maintain a high rate of collagen production independent of cellular proliferation rate (Breul et al. 1980, Kamine & Rubin 1977), and several studies have suggested that glycine and proline availability may be important metabolic requirements of fibroblasts. A reduction in glycine production in fibroblasts through inhibition of phosphoglycerate dehydrogenase (PHGDH), an enzyme involved in serine and glycine synthesis, resulted in reduced collagen production and reduced fibrosis in a pulmonary fibrosis model (Hamanaka et al. 2018, Nigdelioglu et al. 2016). Proline availability from extracellular sources or from proline synthesis can be limiting for collagen synthesis, suggesting that acquisition of this amino acid is a biosynthetic demand of fibroblasts (Finerman et al. 1967, Kershenobich et al. 1970, Phang et al. 1971, Rojkind & Diaz de León 1970). ECM proteins such as collagen produced by fibroblasts can also be taken in by cancer cells and catabolized into amino acids, serving as an alternative nutrient source (Davidson et al. 2017, Muranen et al. 2017, Olivares et al. 2017). Therefore, targeting these metabolic demands of fibroblasts could be a way to limit a source of nutrients for cancer cells.

A primary source of proline for collagen synthesis by fibroblasts in culture is glutamine, suggesting that glutamine metabolism could be an important pathway in fibroblasts (Bellon et al. 1987, Lehtinen et al. 1978). A recent study demonstrated that glutaminase expression was higher in CAFs than in cancer cells in pancreatic tumors and that the CAFs were more sensitive to glutamine withdrawal than cancer cells (Knudsen et al. 2016). Proliferating fibroblasts were more dependent on glutamine metabolism relative to quiescent fibroblasts, which may rely more on pyruvate carboxylase than on glutamine metabolism to support production of tricarboxylic acid (TCA) cycle intermediates (Lemons et al. 2010).

Glutamine synthesis and secretion have also been implicated in fibroblast biology. Compared to normal PSCs, CAFs secrete higher levels of glutamate and glutamine in culture, supporting the growth of pancreatic cancer cells in both coculture and conditioned media experiments (Francescone et al. 2018). Higher levels of glutamine synthetase have also been reported in CAFs as compared to normal fibroblasts or cancer cells (Francescone et al. 2018, Yang et al. 2016), and inhibiting glutamine anabolism in fibroblasts can result in tumor regression (Yang et al. 2016). Further investigation into the role of glutamine metabolism in fibroblasts is needed.

Symbiotic metabolic interactions have been suggested to occur between fibroblasts and cancer cells that favor tumor growth in various cancer types including pancreatic cancer, breast cancer,

and prostate cancer (Linares et al. 2017, Pavlides et al. 2012, Sousa et al. 2016, Valencia et al. 2014). In these models, tumor epithelium induces stromal fibroblasts to become activated CAFs, which then release factors or metabolites important for cancer cell proliferation and metabolism (**Figure 2*a***). For example, in prostate cancer, loss of the scaffolding/adaptor protein p62 in the stroma led to resistance to glutamine deprivation, ultimately resulting in asparagine production by the stroma to support prostate cancer growth (Linares et al. 2017, Valencia et al. 2014). There is also evidence that cancer cells can directly acquire amino acids secreted from fibroblasts that were derived from stromal cell autophagy. Conditioned media from PSCs were found to contain high levels of alanine, which was dependent on PSC autophagy (Sousa et al. 2016). Labeled alanine was incorporated into TCA metabolites and lipids in pancreatic cancer cells, suggesting that alanine secreted by PSCs may contribute to the metabolism of pancreatic cancer cells (Sousa et al. 2016). Stromal cell autophagy has also been shown to supply amino acids to support cancer cell proliferation in a *Drosophila* model (Katheder et al. 2017). Exosomes, vesicles that are secreted from CAFs, are yet another route whereby metabolites can be taken up by cancer cells (Zhao et al. 2016), although the amount of material that can be packaged into exosomes is likely small relative to what is derived from the circulation.

There is accumulating evidence that stromal cells can confer resistance to the chemotherapeutic agent gemcitabine, a deoxycytidine analog that incorporates into DNA and can inhibit DNA synthesis. It has been known for many years that fibroblast-conditioned media can inhibit nucleoside uptake, DNA repair, and cancer cell proliferation (Downes et al. 1983). Gemcitibine has been shown to accumulate more in fibroblasts than in cancer cells in vitro, suggesting a role for drug sequestration by fibroblasts in gemcitabine resistance (Hessmann et al. 2018). In addition, deoxycytidine secretion into conditioned media by fibroblasts (Dalin et al. 2019), as well as by macrophages (Halbrook et al. 2019), can also contribute to cancer cell gemcitabine resistance. Deoxycytidine prevents activation of gemcitabine to the form active in cells, and this reduces the toxicity of cytidine analogs (Buchman et al. 1979).

The so-called reverse Warburg effect is another proposed way that cancer cells and fibroblasts can be metabolically coupled through the sharing of lactate and pyruvate (Pavlides et al. 2009). In this model, cancer cells induce fibroblasts to increase glycolysis and secretion of lactate and pyruvate, which can then be taken up by the cancer cells and used in the TCA cycle to generate energy (Pavlides et al. 2009). This idea was based on the finding that CAFs exhibit aerobic glycolysis and that TGF-β, a known inducer of fibroblast activation, promotes lactate secretion (Racker et al. 1985). This led to a provocative hypothesis that the Warburg effect is in fact a stromal phenomenon (Pavlides et al. 2009). However, this hypothesis is supported primarily by gene or protein expression data of glycolytic enzymes, or pyruvate and lactate transporters, or by inhibiting glycolysis or pyruvate and lactate transport in fibroblasts (Bonuccelli et al. 2010, Migneco et al. 2010, Rae et al. 2009, Whitaker-Menezes et al. 2011, Witkiewicz et al. 2012). The indirect methods used to study this phenomenon highlight the challenges associated with studying nutrient sharing in tumors or culture systems containing mixtures of multiple cell types, and new approaches to test this hypothesis are needed.

When two or more cell types are present in a culture system, it becomes impossible to distinguish the origin of metabolites secreted into the media or stored inside cells. This has led some researchers to focus on the effects of fibroblast-conditioned media on cancer cells, although this approach may not reflect how metabolites are shared when all cell types can simultaneously interact with nutrients in their environment. Isotope labeling studies to trace the fate of nutrients in cells can be challenging to interpret when only one cell type is present, and this is complicated further by the presence of multiple cell types. In the absence of information on net metabolite uptake and secretion, it can be difficult to distinguish between metabolite use and label exchange

into the system despite net excretion of a labeled metabolite (Buescher et al. 2015, Muir et al. 2018). New approaches to delineate metabolism in shared cocultures will be helpful in determining how nutrients are shared between cancer cells and fibroblasts, as well as among any mixtures of cell populations in tumors and other tissues.

T CELL METABOLISM

T lymphocytes, or T cells, are part of the adaptive immune system and orchestrate responses to eliminate cells expressing non-self-antigens. T effector (Teff) cells comprise several subsets of T cells including helper, killer, and regulatory T cells (Tregs), which respond to antigen stimulation. A subset of these cells can differentiate into memory T cells that help to mount a rapid immune response should the same antigen be encountered in the future. Helper T cells are a subset of $CD4^+$ T cells that stimulate cytotoxic T cells and macrophages to eliminate infected cells, while Tregs are another subset of $CD4^+$ T cells that suppress T helper cells to limit the extent of immune responses and prevent autoimmune disease. Cytotoxic, or killer, T cells, also known as $CD8^+$ T cells, are responsible for killing virus-infected cells and cancer cells. Tumors can evade targeting by activated T cells via various mechanisms, including T cell exclusion by the matrix and stromal cells in the tumor microenvironment (Joyce & Fearon 2015), as well as by immune editing, whereby nonimmunogenic cancer cells are selected as the tumor grows (Schreiber et al. 2011).

While aerobic glycolysis is often associated with cancer cell metabolism, it has been appreciated for decades that activated T cells also exhibit aerobic glycolysis (Wang et al. 1976). Upon stimulation, T cells increase nutrient uptake and increase both glycolysis and lactate production (Brand et al. 1988, Frauwirth et al. 2002, MacIver et al. 2008). In fact, lymphocytes are thought to transition from oxidative to glycolytic metabolism during the intense period of proliferation that accompanies T cell activation, and then return to oxidative metabolism when they become quiescent memory T cells (Michalek & Rathmell 2010).

Because both T cells and cancer cells can be highly glycolytic, it has been hypothesized that cancer cells compete with T cells for glucose in the tumor microenvironment (**Figure 2*b***). Glucose has been shown to be depleted in the interstitial fluid of some tumors compared to plasma or healthy tissue (Burgess & Sylvén 1962, Gullino et al. 1964, Ho et al. 2015, Sullivan et al. 2019); however, not all studies have found glucose depletion in tumors (Siska et al. 2017). This suggests that competition for glucose could be limiting for T cells that require high glucose uptake rates in some contexts, and it potentially explains why some cancers can evade the immune response. Low glucose levels can limit T cell function, and enhancing glucose uptake in T cells supports activation (Jacobs et al. 2008). Glucose depletion leads to suppression of T cell activation and may limit antitumor responses (Cham & Gajewski 2005, Cham et al. 2008, Chang et al. 2015, Ho et al. 2015), although aerobic glycolysis is not required for T cell proliferation or survival (Chang et al. 2013). In support of metabolic competition for glucose in the tumor microenvironment, increased expression of the glycolytic enzyme hexokinase 2 (HK2) in cancer cells can result in improved evasion of T cell immune surveillance and increased tumor growth, suggesting a role for the glycolytic intermediate PEP (phosphoenolpyruvate) in promoting Teff cell functions (Ho et al. 2015). Injecting a bolus of glucose into mice has been shown to enhance T cell function, and programmed death ligand 1 (PD-L1), which is expressed on cancer cells and helps cancer cells evade antitumor immunity, can also promote glycolysis (Chang et al. 2015). Studies suggest that artificially restoring PEP levels in T cells could improve anticancer immune response (Ho et al. 2015). They also suggest that targeting glycolysis in cancer could have the disadvantageous effect of blunting the T cell response in tumors. While these data illustrate how competition between

cells in a tumor might affect antitumor immune responses, more work is needed to determine the level of glucose that is limiting for both cancer cells and T cells in vivo, as depleted levels of glucose in interstitial fluid can still be relatively high, in the low-millimolar range (Sullivan et al. 2019).

While Teff cells primarily rely on aerobic glycolysis, Tregs instead rely on oxidative phosphorylation (OXPHOS). Inhibition of OXPHOS in Tregs inhibits their functions. For example, Tregs are more prone to apoptosis in response to oxidative stress and reduced Nrf2 activity (Maj et al. 2017). Induction of apoptosis in Tregs can result in adenosine release, which can bind to receptors on antigen-presenting cells, Teff cells, and cytotoxic T cells to sustain immunosuppression even when these cells are eliminated (Maj et al. 2017). Foxp3, an important transcription factor in Tregs, has been shown to regulate expression of metabolic pathway genes in these cells (Angelin et al. 2017, Gerriets et al. 2016, Howie et al. 2017). Foxp3 reprograms $CD4^+$ T cells and allows them to maintain suppressive function in tumors where there are low glucose concentrations and high lactate concentrations (Angelin et al. 2017). Lactate produced from cancer cells in the tumor microenvironment can also affect immunosurveillance by T cells, as reducing lactate dehydrogenase levels in cancer cells in tumors can result in increased numbers of active $CD8^+$ T cells, whereas increased lactate reduces activation and numbers of $CD8^+$ T cells (Brand et al. 2016). The tumor microenvironment can induce tumor-infiltrating $CD8^+$ T cells to have reduced mitochondrial function and mass, and supporting mitochondrial function in these cells results in improved T cell function (Scharping et al. 2016).

Tregs can also suppress proliferation of Teff cells through effects on complex I of the mitochondrial electron transport chain. Knockout of a component of complex I decreased the suppressive activity of Tregs (Angelin et al. 2017). Foxp3 is also known to upregulate expression of electron transport chain complexes (Howie et al. 2017). Mitochondrial complex III is required for Treg function as well, as knockout of complex III in Tregs results in the development of a lethal inflammatory disorder without affecting T cell numbers or proliferation (Weinberg et al. 2019), further highlighting the importance of the mitochondrial electron transport chain in Treg function.

Amino acids also have important roles in T cell function. Lymphocytes can metabolize glutamine at high rates (Ardawi & Newsholme 1983). Serine plays an important role in T cell expansion, producing glycine and one-carbon units for nucleotide synthesis (Ma et al. 2017). Arginine is another amino acid that has been shown to be important for T cell survival and antitumor activity (Geiger et al. 2016). The dependence of lymphocytes on extracellular asparagine has been known for some time (Berenbaum et al. 1973, Ohnuma et al. 1977, Schrek et al. 1967), as has the role of tryptophan metabolism in regulating immune responses (Moffett & Namboodiri 2003, Routy et al. 2016). Therefore, depletion of amino acids from the tumor microenvironment by cancer cells may be a way to diminish T cell function and contribute to evasion of an anticancer immune response. Since T cell metabolism has many similarities to cancer cell metabolism, fully understanding the nuances of the relationship between these two cell types may lead to insights for the development of novel metabolic therapies that eliminate cancer cells without impacting anticancer immunity, or that improve the immune response to cancer cells.

MACROPHAGE METABOLISM

Macrophages are phagocytic cells that are terminally differentiated and do not have the demands of rapid proliferation like T cells, cancer cells, and some fibroblast populations in tumors. Traditionally, macrophages have been divided into two states based on results from experiments where precursors are stimulated in culture: classically activated (M1) macrophages and alternatively activated (M2) macrophages. Macrophage activation with interferon-gamma (IFN-γ) or

lipopolysaccharide (LPS) leads to the generation of M1-like macrophages that are important for killing, while M2-like macrophages are traditionally derived by exposure to different cytokines and are important for wound healing. M1-like macrophages are the subtype thought to be important for inflammation and killing cancer and bacterial cells, whereas M2-like macrophages are more important for immunosuppression and protumoral activity. However, recently it has become apparent that, similar to other stromal cell types, there is extensive macrophage heterogeneity in vivo and that macrophage cell states exist along a spectrum that depends on the tissue environment and local signals (Lavin et al. 2014, Xue et al. 2014). Therefore, new nomenclature has been proposed in which macrophages are described by a combination of identifying characteristics including source, production method, activating signals, culture conditions, and expression of cell surface markers (Murray et al. 2014). The term "tumor-associated macrophages" (TAMs) is commonly used to refer to macrophages in the tumor microenvironment.

There is contradictory data about whether macrophages are tumor promoting or tumor restricting. Early studies provided evidence that macrophages can restrict tumor growth and led to the idea that macrophages were part of an anticancer immune response. An inverse correlation between tumor macrophage content and the extent of metastasis was found in some tumors (Eccles & Alexander 1974, Wood & Gillespie 1975), and the depletion of macrophages in a tumor was shown to increase metastasis (Wood & Gillespie 1975). Macrophages coinjected subcutaneously with tumor cells can inhibit growth in mice (Picard et al. 1986) as well as metastasis formation (Fidler 1974, Liotta et al. 1977). Conversely, more recent studies have shown that macrophages can also be protumorigenic (Chittezhath et al. 2014). TAMs are proposed to promote a proinflammatory environment to support tumor growth. TAMs can promote metastasis in some contexts, as deleting the macrophage growth factor colony-stimulating factor 1 (Csf-1) in a mouse model of breast cancer did not affect primary tumor growth but delayed the development of invasive and metastatic cancer, whereas overexpression of Csf-1 led to the acceleration of cancer progression (Lin et al. 2001). CSF-1 deletion in pancreatic neuroendocrine cancer inhibits tumor formation (Pyonteck et al. 2012). TAMs have also been suggested to enhance cancer cell survival via AKT signaling (Chen et al. 2011) or to promote metastasis via induction of epithelial-to-mesenchymal transition (Su et al. 2014). Studies on whether macrophage content is correlated with better or worse prognosis are mixed depending on the study and cancer type (Zhang et al. 2012), although more studies indicate that macrophage content is associated with poor prognosis (Bingle et al. 2002). These contradictory results likely reflect differences in both cancer type and macrophage phenotypes. Thus, macrophages appear to play a dual role in the tumor microenvironment, being important for cancer cell removal or tumor growth depending on the context.

Metabolism is remodeled during macrophage activation. It is thought that there is a switch from oxidative metabolism to higher glucose consumption and lactate production during M1-like macrophage activation, whereas the opposite is true of M2-like macrophage activation (Derlindati et al. 2015, Rodríguez-Prados et al. 2010). A proteomics study revealed that glycolytic enzymes are more highly expressed in TAMs compared to bone marrow–derived macrophages (Liu et al. 2017). It has been reported that lactate can polarize macrophages to an M2-like state as measured by gene expression changes (Colegio et al. 2014), and classic studies showed that macrophages can also use glutamine at high rates (Newsholme et al. 1986, 1987).

As noted above, macrophages can secrete deoxycytidine into the tumor microenvironment (Chan et al. 1983, Chan & Lakhchaura 1982, Halbrook et al. 2019) and confer resistance to gemcitabine, providing a mechanism that explains why depletion of TAMS can sensitize tumors to this drug (Halbrook et al. 2019). Itaconate is another metabolite produced by macrophages that has only recently been appreciated for its role in metabolism and immunity. The enzyme responsible for producing itaconate, IRG1, was identified as being upregulated after LPS

treatment of macrophages but had unknown functions for many years (Lee et al. 1995) before several groups identified its role as an enzyme in macrophage itaconate production (Shin et al. 2011, Strelko et al. 2011, Sugimoto et al. 2012). IRG1 produces itaconate by decarboxylating the TCA cycle intermediate *cis*-aconitate (Michelucci et al. 2013), and itaconate inhibits bacterial growth (Michelucci et al. 2013) by inhibiting isocitrate lyase, an enzyme used in the glyoxylate shunt that is not found in mammals (McFadden & Purohit 1977, Patel & McFadden 1978). Reduction of IRG1 in macrophages can reduce tumor growth (Weiss et al. 2018). Itaconate has also been reported to inhibit succinate dehydrogenase and succinate production (Lampropoulou et al. 2016) and can alkylate KEAP1 to activate NRF2 (Mills et al. 2018). Isotope tracing data have revealed that M1 macrophages redirect citrate to itaconate synthesis (Jha et al. 2015). Finally, inhibition in macrophages of branched-chain amino transferase 1 (BCAT1), the enzyme responsible for transamination of branched-chain amino acids, was shown to block itaconate production (Ko et al. 2017). Further work is needed to fully understand the variety of roles that itaconate plays in macrophages and in other immune cells in the tumor microenvironment.

Due to its expression in M2 murine macrophages, the enzyme arginase has been used as a macrophage-specific marker. Arginase catalyzes the conversion of arginine to ornithine and urea. Ornithine can be used to synthesize polyamines, the function of which is incompletely understood but can be important for cell growth (Miller-Fleming et al. 2015). Overexpression of arginase in macrophages increases the growth of cancer cells in coculture, possibly through the production of polyamines (Chang et al. 2001). Transplantation of cancer cells into mice with arginase-deficient macrophages resulted in reduced tumor growth (Colegio et al. 2014). Another possible fate of ornithine is proline production, which can be used for collagen synthesis, as discussed above. It has also been hypothesized that arginase activity and the production of proline via ornithine could be important for collagen production, and there is evidence that collagen is indeed produced by macrophages (Schnoor et al. 2008, Vaage & Harlos 1991, Weitkamp et al. 1999). Macrophages can also be indirectly profibrotic through the secretion of TGF-β, which can activate fibroblasts to induce collagen production. However, depleting arginase in macrophages increases inflammation and fibrosis in mice following pathogen infection, leading to the hypothesis that arginase-expressing macrophages suppress inflammation and fibrosis (Pesce et al. 2009). Another possible role of arginase in macrophages is to reduce the levels of arginine in the tumor environment, which may impair T cell function (Rodriguez et al. 2004). Arginine can also be used to synthesize nitric oxide (NO), an important effector molecule in macrophages (Hibbs et al. 1988, Marletta et al. 1988). Inducible NO synthase (iNOS) catabolizes arginine to NO and citrulline in a reaction that requires NADPH. NO has many reported consequences for the tumor microenvironment, from antimicrobial effects to promoting fibroblast activation. Some cancer cells are arginine auxotrophs (Delage et al. 2010, Ochocki et al. 2018), and thus arginase production by macrophages could similarly restrain the proliferation of cancer cells, particularly as arginine depletion in circulation can restrain the growth of some tumors (Poillet-Perez et al. 2018).

While arginase and NOS have been used as markers of murine macrophages, there is a lack of consensus about whether human macrophages express arginase and produce NO (Thomas 2014). Some studies find evidence for arginase or NOS activity in human monocytes or macrophages (Denis 1991, Kobayashi et al. 2010, Nicholson et al. 1996, Rouzaut et al. 1999), while others do not (Cameron et al. 1990, Munder et al. 2005, Raes et al. 2005, Weinberg et al. 1995). These discrepancies may reflect differences in whether the macrophages were differentiated in vitro from bone marrow or blood monocyte–derived precursors, whether they were isolated from tissue, whether RNA or protein expression or enzyme activity was measured, and whether healthy macrophages or macrophages isolated from diseased or injured tissue were used (Thomas 2014).

Further work is needed to clarify potential differences in arginine metabolism between mouse and human macrophages.

Differences between human and mouse macrophages have also been reported in the response to Toll-like receptor 4 (TLR4) signaling and LPS stimulation (Dorresteijn et al. 2015, Schroder et al. 2012, Vijayan et al. 2019). One study specifically focused on differences in metabolism following LPS stimulation, finding that human macrophages did not switch from oxidative to glycolytic metabolism as measured by oxygen consumption rate and extracellular acidification rate following stimulation (Vijayan et al. 2019).

Another debate surrounding macrophage metabolism centers on the role of fatty acid oxidation in M2 macrophages. Fatty acid oxidation requires carnitine palmitoyltransferase enzymes 1 and 2 (CPT1 and CPT2). In mice, fatty acid oxidation has been shown to be important for the IL-4-induced macrophage response (Vats et al. 2006) via uptake of lipids by the CD36 receptor followed by lipolysis (Huang et al. 2014). However, studies in human macrophages found that fatty acid oxidation was dispensable for the response to IL-4 (Namgaladze & Brüne 2014), and inhibition of fatty acid oxidation with the CPT1 inhibitor etomoxir had a minimal effect on IL-4-induced activation of human or mouse macrophages (Van den Bossche et al. 2016). Myeloid Cpt2 deletion using *Cpt2*$^{fl/fl}$ mice had no effect on IL-4-induced macrophage polarization despite loss of both Cpt2 and fatty acid oxidation (Nomura et al. 2016). Consistent with this finding, etomoxir has been suggested to affect macrophage polarization through CPT-independent metabolic effects, including inhibition of mitochondrial complex I, inhibition of mitochondrial adenine nucleotide transporters, and disruption of coenzyme A homeostasis (Divakaruni et al. 2018, Yao et al. 2018). Similarly, the effects of etomoxir on T cells can also be CPT independent (O'Connor et al. 2018, Raud et al. 2018), highlighting the pitfalls of using this compound to draw conclusions about dependence on fatty acid oxidation. Given the disagreement about the role of arginine metabolism, LPS-stimulated responses, and the importance of fatty acid oxidation in human macrophages, additional studies will be needed to uncover and characterize the metabolic differences between mouse and human macrophages and how this might affect tumor growth in each organism.

ENDOTHELIAL CELL METABOLISM

Endothelial cells line blood vessels and lymphatics, and the generation of new vessels and lymphatics (angiogenesis and lymphangiogenesis, respectively) is important for tumor growth (Dudley 2012). As a tumor grows, it requires new vessels to form and supply the growing tumor with nutrients and oxygen. Accordingly, antiangiogenesis therapies have long been proposed as an anticancer therapy (Folkman 1971); however, although there are several approved antiangiogenic drugs inhibiting the vascular endothelial growth factor (VEGF), they have limited effect on overall patient survival and, in some cases, have resulted in increased metastases (Ebos & Kerbel 2011). Work is ongoing to test whether antiangiogenic drugs can be more effective in some cancers when combined with other therapies such as immunotherapy (Ramjiawan et al. 2017).

It is difficult to isolate pure populations of tumor endothelial cells, as endothelial cell preps are easily contaminated with cancer cells and fibroblasts due to cell nonspecific surface marker expression and the fact that culture conditions for tumor endothelial cells are not well defined (Dudley 2012). Instead, many recent studies have focused on better understanding the metabolic requirements involved when new vessels form, called sprouting.

There are three main categories of endothelial cells: migratory tip cells positioned at the leading edge in vessel sprouting during angiogenesis or lymphangiogenesis, highly proliferative stalk cells that follow the tip cells, and quiescent phalanx cells that line the perfused vessels. Because these different endothelial subtypes have varying proliferative and biosynthetic requirements, they

are also associated with different metabolic states and demands. Endothelial cells are reported to generate most of their ATP from glycolysis (De Bock et al. 2013b). VEGF upregulates PFKFB3 (6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase 3), which then drives glycolysis in endothelial cells and regulates sprouting (De Bock et al. 2013b). Endothelial cells also rely on the serine synthesis pathway. Loss of PHGDH has been shown to reduce angiogenesis in vivo, as well as reduce nucleotide and heme synthesis (Vandekeere et al. 2018). However, while endothelial metabolism has been described as largely glycolytic, mitochondrial complex III is required for endothelial cells to proliferate during angiogenesis, suggesting that mitochondrial respiration is also a vital part of endothelial cell metabolism (Diebold et al. 2019).

Glutamine can play a role in vessel sprouting, as glutamine deprivation or glutaminase inhibition decreases vessel sprouting (Huang et al. 2017). Fatty acid oxidation was also found to be important in proliferating endothelial cells during sprouting (Schoors et al. 2015), as loss of CPT1A decreased vessel sprouting in vitro and in vivo (Schoors et al. 2015). CPT1A knockout also impairs lymphatic vessel development (Wong et al. 2017). Less is known about the quiescent phalanx endothelial cells that line vessels other than that they have lower glycolytic flux compared to proliferating endothelial cells (De Bock et al. 2013b). However, it is hypothesized that since they are exposed to higher oxygen concentrations in the circulation, a major metabolic need would be to limit reactive oxygen species production to lower oxidative damage (De Bock et al. 2013a).

Similar to how cancer cells can induce endothelial cells to begin sprouting, there is evidence that cancer cells can stimulate endothelial cells to increase their glucose uptake for proliferation. For example, conditioned media from hypoxic glioma cells induced endothelial cells to upregulate the expression of the glucose transporter GLUT1 (Yeh et al. 2008). Lactate is also thought to be proangiogenic (Porporato et al. 2012, Ruan & Kazlauskas 2013). TAMs can influence endothelial cells in the tumor microenvironment by regulating tumor blood vessel growth and metastasis. Enhancement of glycolysis in TAMs promoted normalization of blood vessels and inhibited metastasis formation in several tumor models (Wenes et al. 2016). In addition to glucose metabolism, glutamine metabolism may also be involved in metabolic cross talk or competition between endothelial cells and other cells in the tumor microenvironment. Inhibiting glutamine synthetase and glutamine synthesis in TAMs coinjected with cancer cells inhibited endothelial network formation, inhibited metastasis, and reprogrammed macrophages toward an M1-like state (Palmieri et al. 2017). These results support a model in which there is metabolic competition between endothelial cells, macrophages, and cancer cells for glucose in the tumor microenvironment (Zecchin et al. 2017); however, as discussed previously, more work is needed to determine the range of glucose and other nutrients that is limiting for different cells in vivo.

Glycan metabolism has also been implicated in endothelial cell metabolism. Endothelial cells from highly metastatic melanomas were found to secrete the proteoglycan biglycan, which promotes metastasis of cancer cells (Maishi et al. 2016). Metabolomics of ovarian and colon cancer cells cocultured with endothelial cells also revealed alterations in glycan synthesis in cancer cells (Halama et al. 2017).

CONCLUSIONS

Interactions between cancer and stromal cells are difficult to study but can yield valuable insights into the biology and metabolism of tumors. Various culture and in vivo models are moving beyond monocultures of cancer cells to better understand the complex relationships between cancer and stromal cells in the tumor microenvironment. Further understanding the metabolism of tumor stromal cells could lead to the development of novel therapies targeting tumor metabolism. Immunotherapy approaches are one example of non-cancer-cell-autonomous biology being

exploited to prevent tumor growth and demonstrate that therapeutically targeting tumor stromal cells can be an effective strategy to treat cancer. In the future, therapies aimed at modulating the metabolic interactions between cancer cells and various tumor stromal cells may provide additional therapeutic benefit to patients.

SUMMARY POINTS

1. Each stromal cell type is a collection of several different cell subtypes characterized by unique marker expression and function.
2. Tumor heterogeneity and stromal content are often not reflected in metabolic studies using in vitro culture systems.
3. Aerobic glycolysis is a characteristic of not only cancer cells; stromal cells can also exhibit high rates of glycolysis and share other metabolic phenotypes with cancer cells.
4. Fibroblasts in cancer are characterized by high rates of glycolysis and ECM production.
5. T cell subsets exhibit different rates of glycolysis and oxidative metabolism.
6. Metabolism can influence the activation state of macrophages.
7. Endothelial cells rely on several nutrients and pathways for vessel sprouting.

FUTURE ISSUES

1. New approaches are needed to tease apart the metabolism of individual cell types in heterogeneous cell mixtures.
2. New approaches are needed to understand symbiotic relationships between various tumor cell types.
3. How different or similar are mouse and human stromal cells?
4. Under what contexts do various stromal cell types restrain versus promote tumor growth and progression?
5. What metabolic characteristics are unique to cancer cells or specific stromal cells?
6. What metabolites are limiting in the tumor microenvironment, resulting in metabolic competition between cell types that affects their function?

DISCLOSURE STATEMENT

M.G.V.H. is a consultant and scientific advisory board member for Agios Pharmaceuticals, Aeglea Biotherapeutics, and Auron Therapeutics.

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